What's New in Perinatal Research?
U.S. and International Update

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[*Note: A number of the ideas in this presentation are also in a paper which will be published shortly in a supplement to the journal* Trophoblast Research.]

U.S. Update

The incidence of perinatally-acquired AIDS in the United States has shown an 81% decline as of June 2000 (reports through December 2000) from its all-time high in 1992. The Women and Infants Transmission Study (WITS) and other studies have demonstrated that the decline in perinatal transmission in the study population is associated with use of perinatal antiretroviral treatment, especially since 1994.

A. Dorenbaum reported the results of PACTG 316 at the 8th Conference on Retroviruses and Opportunistic Infections (Abstract LB7) in February of this year: "Among HIV-infected women who receive prenatal care and who are treated with standard ARV prophylaxis (generally combination therapy), the risk of perinatal transmission is low (1.5%; 95% CI 1.0-2.7%). Administration of the 2-dose NVP prophylaxis regimen did not further reduce transmission in this setting."

We have seen an increase in the percentage of HIV-infected pregnant women undergoing cesarean section in the U.S. to around 44% in 2000 (The Pediatric Spectrum of Disease study), a practice which seems to decrease risk of perinatal transmission. This percentage is still lower than that seen in Europe and Brazil.

Reduction of perinatal HIV transmission below 1% in the U.S. seems feasible. The remaining U.S. groups at risk for perinatal HIV transmission include:

- late presenters without prenatal care
- women seen in antenatal care but not offered voluntary counseling/testing due to perceived low risk
- HIV-infected pregnant women who were prescribed but did not take antiretrovirals
- unexplained "failures."

Determining the timing of perinatal HIV infection is of great clinical relevance for implementing cost-effective prophylaxis. A recently published study (Kourtis AP, et al. *JAMA* 2001; 285:709-12) proposes a model for the approximate temporal distribution of mother-to-infant transmission (in non-breastfeeding populations) based on findings from recent studies, arguing that most HIV infections occur very late in gestation. Estimations suggest that most transmission occurs during the last few days of pregnancy.

This table provides a summary of current knowledge on factors affecting mother-to-child HIV-1 transmission.

Known risk factors
High maternal viral load
Viral genotype/phenotype
Advanced maternal HIV disease
Low CD4 count or percent
Vaginal delivery
Duration of membrane rupture > 4 hours
Premature delivery (< 37 weeks)
Breastfeeding

Factors for which evidence is suggestive but not conclusive
Genetic factors
Immature immune system in infant
Increased viral strain diversity
Maternal neutralizing antibody
Illicit drug use during pregnancy
Frequency of unprotected sexual intercourse
Multiple sex partners during pregnancy
Maternal nutritional status
Anemia during pregnancy
Cigarette smoking
Chorioamnionitis
Abruptio placentae
Placental *P. falciparum* infestation
Syphilis and other STD
Fetal scalp electrodes
Episiotomy and vaginal tears

Of the known risk factors, how important is maternal viral load?

- Maternal HIV-1 RNA level is strongly correlated with risk of transmission.
- RNA level near the time of delivery is an important predictor of transmission even among ARV-treated women.
- Most studies do not find a threshold below which no transmission occurs.
- The 076 zidovudine regimen appears to be protective at all levels of maternal RNA (ACTG 076 findings).

Transmission rates by plasma viral load at time of delivery were studied in Bangkok, Thailand by N. Shaffer, et al. (*Journal of Infectious Diseases* 1999 Mar;179(3):590-9). Although risk is multifactorial, they found that "high maternal virus load at delivery strongly predicts transmission."

A recently published meta-analysis (Ioannidis JP, et al. *Journal of Infectious Diseases* 2001; 183(4):539-45) determined that transmission in women with RNA<1000 copies/ml was lower with antiretroviral treatment, cesarean section, greater birth weight, and higher CD4 cell count The authors concluded that:

- Perinatal HIV-1 transmission occurs in only 1% of treated women with RNA virus loads <1000 copies/ml at delivery.
- Antiretroviral treatment reduces the risk of transmission even in women with RNA < 1,000 copies/ml at delivery and when adjusting for potential confounders. This protective effect seems to operate above and beyond the lowering of maternal viral load.

Host genetic factors and perinatal HIV transmission is currently a topic of great interest. What do we know about it?

- Immunogenetic mechanisms facilitating protection of approximately 75% of HIV-exposed

infants are still poorly understood.

- Data from Kenya suggest that Class I HLA mother-infant concordance is associated with increased risk of transmission (MacDonald KS, et al. *Journal of Infectious Diseases* 1998 Mar;177(3):551-6); also independent effect of HLA supertype A2/6802 (MacDonald KS, et al. *Journal of Infectious Diseases* 2000 May;181(5):1581-9).
- Association of Class II HLA homozygocity with transmission as well as disease progression was shown in PACTS case-control study (as yet unpublished data)
- Polymorphisms in the regulatory regions of CCR5 may also influence transmission (Kostrikis LG, et al. *Journal of Virology* 1999 Dec;73(12):10264-71).

Maternal sexual behavior may be related to mother-to-child HIV-1 transmission. In two African cohort studies, investigators reported a higher risk of vertical HIV-1 transmission related to unprotected sexual intercourse with multiple partners (Bulterys M, et al. *AIDS* 1993 Dec;7(12):1639-45; Lallemant M, et al. *AIDS* 1994 Oct;8(10):1451-6). In Italy, mother-to-child transmission was more frequent among concordant HIV-positive mother-father couples (Galli L, et al. *Pediatric AIDS and HIV Infection: Fetus to Adolescent* 1993; 4:425-8.). In New York, frequency of unprotected intercourse during pregnancy was strongly associated with HIV mother-to-child transmission (Matheson PB, et al. *AIDS* 1996 Sep;10(11):1249-56).

In an article entitled "From biology to sexual behavior--towards the prevention of mother-to-child transmission of HIV," (*AIDS* 1996 Sep;10(11):1287-9), I and my co-author argued that promotion of safer sexual practices and improved treatment of STD may be widely applicable public health strategies to reduce mother-to-child transmission. Unsafe sexual practices and poor or no treatment of STDs might increase risk of vertical transmission through such plausible pathophysiological mechanisms as: a) HIV-1 concentration or strain diversity; b) inflammation of the cervix or vagina by microabrasions or sexually transmitted infections; and c) chorioamnionitis or reduced placental integrity.

Another research question of current interest is whether mother-to-child HIV-1 transmission rates are decreasing over time. Even in the absence of antiretroviral prophylaxis, mother-to-child transmission rates appear to decrease over time in many locations (e.g., Bangkok, Kampala, Miami, Nairobi, New York City). Possible explanations as to why the highest mother-to-child transmission rates occur during the early years of epidemic HIV-1 spread include: a) bias due to differential infant follow-up; b) changes in obstetric practice; c) changes in the proportion of women with advanced HIV disease or incident HIV infection; d) host genetics--women at highest risk for mother-to-child transmission become infected first; and e) the possibility of viral attenuation over time.

What does recent research tell us about the role of neonatal antiretroviral prophylaxis in reducing the risk of perinatal HIV transmission? Studies from sub-Saharan Africa and New York state and data from CDC's Perinatal AIDS Collaborative Transmission Study (PACTS) allow us to draw the following conclusions:

- Neonatal prophylaxis starting in labor through 1st week of life reduces transmission in breastfeeding settings.
- Intrapartum ZDV/3TC alone is not sufficient.
- 2 neonatal doses of PMPA can protect newborn macaques against SIV infection.
- 6 weeks of neonatal ZDV can be effective in non-breastfeeding settings, if started within 12-24 hours after birth.
- Optimal duration of prophylaxis for breastfed and non-breastfed infants remains unclear.

CDC's Mother-Infant Rapid Intervention At Delivery project (MIRIAD) will start a new protocol in 5 U.S. cities (Atlanta, Chicago, Miami, New Orleans, and New York) as soon as IRB review is completed. The objectives of the MIRIAD project are to:

- evaluate innovative approaches to counseling and voluntary rapid HIV testing for women in labor with unknown HIV status
- assess feasibility of obtaining informed consent during labor or soon after birth
- describe barriers to HIV testing and reasons for lack of prenatal care
- assess rapid delivery of ARV prophylaxis to late presenters
- evaluate neonatal therapy adherence; and receipt of post-natal care for women identified as HIV-infected.

Update: International Perinatal HIV Research Progress

Short-course antiretroviral trials show that peripartum ZDV and nevirapine (NVP) regimens remain efficacious despite ongoing transmission through breastfeeding. However, recent studies have detected the presence of maternal resistant mutations to NVP and 3TC at 6 weeks postpartum and NVP resistance in infants who became infected despite NVP prophylaxis.

Embree, et al. (*AIDS* 2000 Nov 10;14(16):2535-41) identified the following clinical risk factors for HIV-1 transmission through breastfeeding in Nairobi:

- primary HIV-1 infection during lactation
- high plasma and breast milk viral load
- prolonged duration of breastfeeding (>15 months)
- clinical and subclinical mastitis, breast abscesses
- thrush in the infant.

Also in Nairobi, GC John, et al. (*Journal of Infectious Diseases* 2001 Jan 15;183(2):206-12) identified correlates of early vs. late infant HIV-1 infection:

Early Infection (<2 months of age):
Viral load (plasma RNA, cervical or vaginal DNA)
Cervical or vaginal ulcers
CD4 count <200
Prematurity
Breastfed
Bleeding nipples

Late Infection (> 2 months of age):
Maternal plasma RNA >43,000
Mastitis
Breast abscess.

Several clinical trials on reducing rates of HIV transmission through breastfeeding are being planned in Africa and India. These will include: infant ARV prophylaxis trials; vaccine and passive immune trials;

exclusive breastfeeding; and early and abrupt weaning. However, a soon-to-be-published study (in *Lancet)* showed that mortality among HIV-infected women in Nairobi was significantly higher in breastfeeding than in formula-feeding women.

Implementation of international perinatal HIV prevention faces many challenges:

- sharp increases in seroprevalence during adolescent years, particularly among female youth
- high HIV prevalence among pregnant women
- inadequate antenatal voluntary counseling and testing (VCT) infrastructure
- reversal, related to HIV, in infant survival gains
- breastfeeding transmission
- competing health priorities in face of scarce resources.

The magnitude of the problem is enormous. An estimated 620,000 children were newly infected with HIV during 1999; 515,000 of these in sub-Saharan Africa.

CDC sponsors a number of perinatal HIV prevention activities in Kenya:

- implementation of single-dose NVP at Kisumu Provincial Hospital, Nyanza Province
- planned expansion to local district health centers and traditional birth attendants in Asembo Bay, Nyanza
- follow-up of mother-infant cohort to assess the impact of placental malaria on perinatal HIV transmission
- an integrated approach to improving child survival
- technical assistance to the Ministry of Health (LIFE initiative).

A successful international model of perinatal HIV prevention is found in Thailand. Elements of this successful model include:

- built on short-course ZDV trial results
- government commitment
- well-organized antenatal infrastructure including VCT
- successful pilot projects being expanded to national level
- next steps include identifying women needing treatment.

In summary, the main research challenges in global prevention of perinatal HIV infection are:

- primary prevention of HIV among youth
- decreasing transmission through breast milk, and
- operational research on implementation of short-course ARV interventions.

Conclusion

Two perinatal HIV-1 epidemics exist. There has been dramatic progress in the U.S. and Europe in research and implementation. There has also been progress in international research, but there are major implementation challenges in the developing world. Integrated maternal-and-child-health approaches to improve child survival are urgently needed.